Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update

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The full text of the updated recommendations is available online (www.cmaj.ca/cgi/content/full/169/9/921/DC1)

Clinical practice guidelines require continual reassessment in response to new information and changes in the pattern of disease. Challenges in Canada, as in all industrialized countries, include the increasing size of the elderly population and the rising prevalence of obesity and diabetes mellitus. More than 20% of Canadians will be over 65 years of age by 2011. Obesity, particularly abdominal adiposity, is associated with an increased prevalence of diabetes, hypertension and other features of the metabolic syndrome (hypertriglyceridemia, low levels of high-density lipoprotein cholesterol [HDL-C] and insulin resistance). Currently, 31% of Canadian adults are obese (defined as a body mass index greater than 27 kg/m^2). Type 2 diabetes is a major risk factor for coronary artery disease, and its prevalence is reaching epidemic proportions. The First Nations population, with a risk of diabetes 3 to 5 times higher than that of the general Canadian population, is at particular risk.

Because of the burden of cardiovascular disease and the high rate of death from out-of-hospital acute myocardial infarction, preventive measures are essential in order to reduce health care costs and improve the health of Canadians. The Working Group on Hypercholesterolemia and Other Dyslipidemias issued recommendations for the management and treatment of dyslipidemias in Canada in 2000.[1] Since the publication of these Canadian guidelines and of the US National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) report,[2] in 2002, the findings from several important clinical trials have been reported, including those from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study,[3] the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT)[4] and the Heart Protection Study (HPS).[5] As a result, the working group was reconvened to assess this new information and to address the increasing prevalence of the metabolic syndrome and its effect on the risk of cardiovascular disease. In this article, we summarize the working group's revised set of guidelines (see the appendix). (The full text of the updated recommendations is available online at www.cmaj.ca/cgi/content/full/169/9/921/DC1.) The main purpose of the guidelines is to provide primary care physicians and internists with a tool for evaluating a patient's risk of coronary artery disease as part of a routine health assessment.

The revised guidelines have been simplified and include 3 levels of risk of coronary artery disease (high, moderate and low) and 2 treatment targets (the low-density lipoprotein cholesterol [LDL-C] level and the total cholesterol: HDL-C ratio). The US NCEP ATP-III guidelines also provide 3 levels of risk based on the Framingham Study equation but, in contrast to the Canadian guidelines, recommend the use of non-HDL-C levels (i.e., the sum of very-low-density lipoprotein cholesterol and LDL-C levels) as its secondary therapeutic goal, especially in patients with features of the metabolic syndrome. Because the total cholesterol:HDL-C ratio is a more sensitive and specific index of cardiovascular risk than total cholesterol, the working group has chosen this simple lipid ratio as a secondary goal of therapy. Topics specifically addressed in the revised guidelines include the management of patients at high risk of coronary artery disease who have an LDL-C level at target (2.5 mmol/L), the management of patients who have combined dyslipidemia and low HDL-C levels, and the noninvasive assessment of cardiovascular disease and other risk factors, including the metabolic syndrome and levels of apolipoprotein B, lipoprotein(a), homocyst(e)ine and C-reactive protein.

For the 2000 Canadian guidelines, the Framingham Study risk equations used by the working group were those published by Grundy and colleagues.[6] The NCEP ATP-III used an adaptation of Framingham data based on the estimated 10-year risk of "hard cardiac endpoints." These include death from coronary artery disease and nonfatal myocardial infarction. The NCEP ATP-III risk estimate tables also adjust certain risk factors (e.g., total cholesterol level and smoking status) for age and correct for the effect of treatment on blood pressure measurement. This represents a refinement to the previously pub-

lished risk assessment tables. For these reasons and in order to harmonize cardiovascular risk assessment across North America, the working group has used the NCEP ATP-III risk estimation algorithm[2] in the revised guidelines. The presence of diabetes is generally considered as a coronary artery disease risk equivalent.

In addition to their attempt to harmonize cardiovascular risk assessment across North America, the updated guidelines will provide a background recommendation for Canadian specialty organizations such as the Canadian Hypertension Society, the Canadian Diabetes Association, the Dietitians of Canada and the Canadian Society of Atherosclerosis, Thrombosis and Vascular Biology. The guidelines were reviewed by 2 expert panels that included recognized specialists in the areas of cardiovascular disease prevention, lipid metabolism and diabetes as well as primary care physicians. In addition, several medical professional associations had an opportunity to review and comment on this document.

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References

1. Fodor JG, Frohlich JJ, Genest JJG Jr, McPherson PR, for the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management and treatment of dyslipidemia: report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. *CMAJ* 2000;162(10):1441-7.
2. Grundy SM, Becker D, Clark LT, on behalf of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*. Bethesda (MD): National Institutes of Health; 2002. Available: www.nhlbi.nih.gov/guidelines/cholesterol/index.htm (accessed 2003 Sept 26).
3. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al, on behalf of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285(13):1711-8.
4. Robins SJ, Collins D, Rubins HB. Relation of baseline lipids and lipid changes with gemfibrozil to cardiovascular endpoints in VA-High-Density Lipoprotein Intervention Trial (VA-HIT). *Circulation* 1999;100(18)(Suppl I):I-238.
5. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
6. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999;100(13):1481-92.

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Appendix: Summary of recommendations for the management of dyslipidemias and the prevention of cardiovascular disease

Global risk assessment

Risk assessment: A given patient's 10-year risk of coronary artery disease can be estimated using the model on page 924. The 3 categories of risk and corresponding target lipid levels are outlined in Table 1.

Screening: Routinely screen men over 40 years of age and women who are postmenopausal or over 50 years of age. In addition, screen those with: diabetes mellitus; risk factors such as hypertension, smoking or abdominal obesity; a strong family history of premature cardiovascular disease; manifestations of hyperlipidemia (e.g., xanthelasma, xanthoma or arcus corneae); or evidence of symptomatic or asymptomatic atherosclerosis. Patients of any age may be screened at the discretion of the physician, particularly when lifestyle changes are indicated.

Factors influencing risk assessment

Metabolic syndrome: The clustering of cardiovascular risk factors is recognized as being an important health issue. The metabolic syndrome is defined in qualitative terms and encompasses abdominal obesity, insulin resistance, elevated plasma triglyceride levels, low HDL-C levels and high blood pressure (Table 2).

Apolipoprotein B: Plasma apolipoprotein B measurement may be of particular utility in determining cardiovascular risk and adequacy of treatment in people who have the metabolic syndrome. An optimal level of apolipoprotein B in a patient at high risk of coronary artery disease is less than 0.9 g/L.

Lipoprotein(a): A lipoprotein(a) concentration greater than 30 mg/dL in a patient who has a total cholesterol:HDL-C ratio greater than 5.5 or other major risk factors may indicate the need for earlier and more intensive therapy to lower the LDL-C level.

Homocyst(e)ine: There is insufficient evidence to warrant broad homocyst(e)ine screening until the results of ongoing clinical trials show that vitamin supplementation to lower homocyst(e)ine levels decreases cardiovascular risk.

High-sensitivity C-reactive protein: Measurement of high-sensitivity C-reactive protein may be clinically useful in identifying people who are at a higher risk of cardiovascular disease than that predicted by a global risk assessment, in particular those with a calculated 10-year risk between 10% and 20%.

Genetic risk: When a family history of coronary artery disease (presenting before age 60) can be ascertained unambiguously, the risk for first-degree relatives is increased by 1.7 to 2.0.

Hormone replacement therapy: Oral hormone replacement therapy does not reduce and may increase cardiovascular disease risk.

Table 1: Risk categories and target lipid levels

Risk category	Target level: LDL-C level, mmol/L	Target level: Total cholesterol: HDL-C ratio
High* (10-year risk of coronary artery disease 20%, or history of diabetes mellitus or any atherosclerotic disease)	< 2.5 ***and***	< 4.0
Moderate (10-year risk 11%–19%)	< 3.5 ***and***	< 5.0
Low (10-year risk 10%)	< 4.5 ***and***	< 6.0

Note: LDL-C = low-density lipoprotein cholesterol.
*Apolipoprotein B can be used as an alternative measurement, particularly for follow-up of patients treated with statins. An optimal level of apolipoprotein B in a patient at high risk is < 0.9 g/L, in a patient at moderate risk < 1.05 g/L and in a patient at low risk < 1.2 g/L.
Includes patients with chronic kidney disease and those undergoing long-term dialysis.
In the "very low" risk stratum, treatment may be deferred if the 10-year estimate of cardiovascular disease is < 5% and the LDL-C level is < 5.0 mmol/L.

Table 2: Clinical identification of the metabolic syndrome*

Risk factor	Defining level
Abdominal obesity	
Men	Waist circumference > 102 cm
Women	Waist circumference > 88 cm
Triglyceride level	1.7 mmol/L
HDL-C level	
Men	< 1.0 mmol/L
Women	< 1.3 mmol/L
Blood pressure	130/85 mm Hg
Fasting glucose level	6.2–7.0 mmol/L

*Criteria: 3 or more of the risk factors.

Diagnosis of asymptomatic atherosclerosis

Atherosclerosis may be detected and the diagnosis of cardiovascular disease confirmed using the following methods:

- *Recommended:* physical examination; ankle–brachial index.
- *Possibly useful in subjects at moderate risk:* Carotid ultrasonography (may detect clinically unapparent atherosclerosis); electrocardiography; graded exercise testing in men over 40 years who have risk factors.
- *Not currently recommended, based on available evidence:* Flow-mediated vasodilatation, plethysmography, arterial compliance; electron beam CT scanning; MRI scanning; intravascular ultrasonography.

Table 3: Current lipid-lowering medications

Drug	Recommended daily dose
Statins	
Atorvastatin (Lipitor)	10–80 mg
Fluvastatin (Lescol)	20–80 mg
Lovastatin (Mevacor)	20–80 mg
Pravastatin (Pravachol)	10–40 mg
Rosuvastatin (Crestor)	10–40 mg
Simvastatin (Zocor)	10–80 mg
Resins (bile acid sequestrants)	
Cholestyramine (Questran)	2–24 g
Colestipol (Colestid)	5–30 g
Cholesterol absorption inhibitors	
Ezetimibe (Ezetrol)	10 mg
Fibrates*	
Bezafibrate (Bezalip)	400 mg
Fenofibrate (Lipidil)	67–200 mg
Gemfibrozil (Lopid)	600–1200 mg
Niacin	
Nicotinic acid	1–3 g

*Avoid in patients with renal insufficiency. Do not use gemfibrozil in combination with statins. Use with caution in patients with diabetes or glucose intolerance.

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Treatment

Diet: An important focus should be on decreasing energy consumption, in particular by reducing intake of refined carbohydrates and sugar to achieve and maintain a body mass index of less than 27.

Medication: In people at high risk of coronary artery disease, treatment should be started immediately, concomitant with diet and therapeutic lifestyle changes. The priority for treatment is reduction of the LDL-C level to less than 2.5 mmol/L and the total cholesterol:HDL-C ratio to less than 4.0. In light of the new data from the Heart Protection Study,[5] the working group recommends that people at high risk be treated with the equivalent of 40 mg/d of simvastatin, with a minimum target level for LDL-C of 2.5 mmol/L. A summary of currently used lipid-lowering medications is shown in Table 3.

Model for estimating the 10-year risk of coronary artery disease in a patient without diabetes mellitus or clinically evident cardiovascular disease, using data from the Framingham Heart Study[6]

MEN

Risk factor	Risk points
Age group, yr	
20–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Total cholesterol level, mmol/L	Age group, yr				
	20–39	40–49	50–59	60–69	70–79
< 4.14	0	0	0	0	0
4.15–5.19	4	3	2	1	0
5.20–6.19	7	5	3	1	0
6.20–7.20	9	6	4	2	1
≥ 7.21	11	8	5	3	1

Smoker	
No	0
Yes	8

HDL-C level, mmol/L	
≥ 1.55	–1
1.30–1.54	0
1.04–1.29	1
< 1.04	2

Systolic blood pressure, mm Hg	Untreated	Treated
< 120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥ 160	2	3

Total risk points	10-year risk, %
< 0	< 1
0–4	1
5–6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥ 17	≥ 30

10-year risk:
_____ %

WOMEN

Risk factor	Risk points
Age group, yr	
20–34	–7
35–39	–3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Total cholesterol level, mmol/L	Age group, yr				
	20–39	40–49	50–59	60–69	70–79
< 4.14	0	0	0	0	0
4.15–5.19	4	3	2	1	1
5.20–6.19	8	6	4	2	1
6.20–7.20	11	8	5	3	2
≥ 7.21	13	10	7	4	2

Smoker	
No	0
Yes	9

HDL-C level, mmol/L	
≥ 1.55	–1
1.30–1.54	0
1.04–1.29	1
< 1.04	2

Systolic blood pressure, mm Hg	Untreated	Treated
< 120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥ 160	4	6

Total risk points	10-year risk, %
< 9	< 1
9–12	1
13–14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥ 25	≥ 30

10-year risk:
_____ %